

U.S. Application Serial No. 09/814,338
Inventors: Jonathan M. Rothberg, *et al*

Attorney Docket No. 21465-501 CIP2

Amendment to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-55. (Cancelled)

56. (Currently amended) A substrate for analyzing a nucleic acid, the substrate comprising:

a cavitated fiber optic wafer formed from a fused bundle of a plurality of individual optical fibers, each individual optical fiber having a diameter between 3 and 100 μm , the wafer comprising a top surface and a bottom surface, the top surface comprising at least 10,000 wells, wherein said wells are etched into the top surface of the cavitated fiber optic wafer and wherein the thickness of the wafer between the top surface and the bottom surface is between 0.5 mm and 5.0 mm in thickness; wherein the depth of each well ranges from between one half the diameter of an individual optical fiber and three times the diameter of an individual optical fiber; and wherein a plurality of wells on the top surface of the cavitated wafer have a nucleic acid therein; and

a plurality of beads within wells on the top surface of the cavitated wafer, said beads having a pyrophosphate sequencing reagent attached thereto.

57. (Currently amended) The substrate of claim 56, wherein the nucleic acid is immobilized on the wells or ~~on said~~ onto beads.

58. (Currently amended) The substrate of claim 56, wherein the diameter of each individual optical fiber in the cavitated wafer is between 6-50 μm .

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59. (Currently amended) The substrate of claim 58, wherein the fiber optic surface includes two or more nucleic acids separated by approximately 10 μm to approximately 200 μm .

60. (Currently amended) The substrate of claim 58, wherein the fiber optic surface includes two or more nucleic acids separated by approximately 10 μm to approximately 150 μm .

61. (Currently amended) The substrate of claim 58, wherein the fiber optic surface includes two or more nucleic acids separated by approximately 150 μm .

62.-63. (Cancelled)

64. (Previously presented) The substrate of claim 56 wherein the wafer further comprises 10^3 or more groups of nucleic acid sequences in said wells.

65. (Currently amended) The substrate of claim 64, wherein said substrate comprises 10^4 or more different groups of nucleic acid sequences in discrete ~~known~~ regions.

66. (Currently amended) The substrate of claim 64, wherein said substrate comprises 10^5 or more different groups of nucleic acid sequences in discrete ~~known~~ regions.

67. (Currently amended) The substrate of claim 64, wherein the nucleic acid sequences are attached to the wells or onto beads by a linker.

68. (Currently amended) The substrate of claim 64, wherein the nucleic acid sequences are covalently attached to the wells or onto beads.

69.-83. (Cancelled)

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84. (Currently amended) An apparatus for processing a plurality of nucleic acids, the apparatus comprising:

a flow chamber having disposed therein a cavitated fiber optic wafer;

a cavitated fiber optic wafer formed from a first fused bundle of a plurality of individual optical fibers, each individual optical fiber having a diameter between 3 and 100 μm , the wafer comprising a top surface and a bottom surface, the bottom surface being highly polished to allow for optical coupling to a second fused bundle of optical fibers, and the top surface comprising at least 10,000 wells, wherein said wells are etched into the top surface of the cavitated fiber optic wafer and wherein the thickness of the wafer between the top surface and the bottom surface is between 0.5 mm and 5.0 mm in thickness; wherein the depth of each well ranges from between one half the diameter of an individual optical fiber and three times the diameter of an individual optical fiber; and wherein a plurality of wells on the on the top surface of the cavitated wafer have a nucleic acid therein;

a plurality of beads within wells on the top surface of the cavitated wafer, said beads having a pyrophosphate sequencing reagent attached thereto;

fluid means for delivering additional pyrophosphate sequencing reagents, including sequential delivery of nucleotide triphosphates, from one or more reservoirs to the flow chamber so nucleic acids in the wells on the top surface of the fiber optic wafer are exposed to the reagents; and

detection means for detecting optical signals from each well, wherein said detection means is in communication with the wells, each optical signal being indicative of reaction of the pyrophosphate sequencing reagents with the nucleic acid in a well.

85. (Currently amended) The apparatus of claim 84, wherein the diameter of each individual optical fiber in the cavitated wafer is between 6-50 μm .

86. (Previously presented) The apparatus of claim 85, wherein said detection means is a CCD camera.

87. (Previously presented) The apparatus of claim 84, wherein the nucleic acid is DNA.

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88. (Previously presented) The substrate of claim 56 wherein the substrate has a polished fiber optic surface opposite to the cavitated fiber optic surface.

89. (Previously presented) The substrate of claim 88 wherein the polished surface allows for optical coupling to a second optical fiber.

90. (Previously presented) The substrate of claim 56 wherein the cavitated fiber optic wafer is coated.

91. (Previously presented) The substrate of claim 90 wherein the coating is selected from the group consisting of plastic, gold layers, organosilane reagents, photoreactive linkers, hydrophilic polymer gels and pluronic polymers.

92. (Previously presented) The substrate of claim 56 wherein said pyrophosphate sequencing reagent is luciferase.

93. (Previously presented) The substrate of claim 56 wherein said pyrophosphate sequencing reagent is sulfurylase.

94.-95. (Cancelled)

96. (Previously presented) The apparatus of claim 84 wherein the cavitated fiber optic wafer is coated.

97. (Previously presented) The apparatus of claim 96 wherein the coating is selected from the group consisting of plastic, gold layers, organosilane reagents, photoreactive linkers, hydrophilic polymer gels and pluronic polymers.

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98. (Previously presented) The apparatus of claim 84 wherein said pyrophosphate sequencing reagent is luciferase.

99. (Previously presented) The apparatus of claim 84 wherein said pyrophosphate sequencing reagent is sulfurylase.

100. (Currently amended) The apparatus of claim 84, wherein the nucleic acid is immobilized on the wells or ~~on said~~ onto beads.

101. (New) The substrate of claim 56, wherein the nucleic acid is DNA.

102. (New) The substrate of claim 56, wherein said pyrophosphate sequencing reagent is luciferase.

103. (New) The substrate of claim 56, wherein said pyrophosphate sequencing reagent is sulfurylase.